REMARKS/ARGUMENTS

Application Status

Claims 1-20 were pending in the subject application. Claims 1-20 were rejected. No claims were allowed. Claims 5 and 20 were objected to for grammatical informalities. Claim 7 was objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 1, 7-9, and 13-19 were rejected under 35 U.S.C. §102(b) and claims 2-6, 10-12, and 20 were rejected under 35 U.S.C. §103(a).

By this amendment, claims 4-6 and 20 have been revised and claim 7 has been canceled. Therefore, claims 1-6 and 8-20 are now pending and before the examiner for consideration.

Claim Objections

In the Office Action, claims 5 and 20 were objected to for informalities, and claim 7 was objected to as being of improper dependent form. Claims 5 and 20 have been amended solely to correct the informalities. Although applicants do not necessarily agree with the examiner's objection to claim 7, to expedite prosecution of the application, claim 7 has been canceled. Claims 5 and 20 are now believed to be in proper form. Withdrawal of these objections is respectfully requested.

Rejections Under U.S.C. §102

The Office Action rejected claims 1, 7-9, and 13-19 under 35 U.S.C. 102(b) for allegedly being anticipated by WIPO Document No. 99/10535 to Liu et al. ("Liu"). The Office Action stated:

> Although Liu '535 does not define the steps contemplated by Applicant in the same manner that Applicant defines these steps, Liu '535 inherently discloses all of the limitations of the Applicant's claims.

Applicants respectfully disagree with this conclusion and note that the present claims each include limitations not expressly or inherently disclosed by Liu. Moreover, the Liu reference does not anticipate the presently claimed invention because it does not enable what the Office Action alleges is anticipated.

The present specification describes experiments that actually show how an *in vitro* stem cell culture system can be used to identify substances that promote tissue-specific differentiation. In particular, expression of genes involved in the differentiation of stem cells along an hepatocyte lineage was assessed at different time points in a culture of embryonic stem cells that had been exposed to various agents that promoted such differentiation. The experiments showed that this system actually produced data sufficiently significant for use in a drug screening system as contemplated by the invention.

In contrast, the experiments described in Liu that were actually carried out were limited to generating gene expression profiles from isolated hematopoetic stem cells from 6-12 week old mice. These experiments did not include the performance of even a single step of independent claim 1. Specifically the experiments did not include a step of providing a library of test substances (claim 1, step A), providing an *in vitro* culture of stem cells (claim 1, step B), contacting subcultures of the culture with a test substance from the library (claim 1, step C), culturing the subcultures under conditions that would promote tissue-specific differentiation of the stem cells if an agent that promoted tissue-specific differentiation was in contact with the stem cells (claim 1, step D), or analyzing the cells in the subcultures for <u>increased</u> tissue-specific gene expression (claim 1, step E).

Although Liu states that its invention includes "...methods to identify a therapeutic agent that modulates the expression of at least one stem cell gene associated with the differentiation,

proliferation and/or survival of stem cells" (Abstract), it does not provide (a) any working examples of such methods or (b) provide sufficient teaching to enable one of skill in the art to successfully practice such methods without undue experimentation. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003), Bristol-Myers Squibb v. Ben Venue Laboratories, Inc. 246 F.3d 1368, 1374, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001), and PPG Industries, Inc. v. Guardian Industries Corp., 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996). The bulk of the specification of Liu is devoted to teaching methods for analyzing gene expression in a cell and to isolating adult hematopoietic stem cells. The description of methods for identifying a therapeutic agent that modulates expression of stem cell genes associated with the differentiation, proliferation and/or survival of stem cells spans 31 lines (page 17 and the first 2 lines of page 18). Nowhere in this section (nor for that matter anywhere within the entire 65 page Liu application) is there mention or suggestion of an *in vitro* culture step.

To arrive at the §102 rejection, the Office Action states that Liu "...inherently discloses all the limitations of Applicant's claims (rejected under this section)." With regard to the *in vitro* culture limitation, the Office Action states:

> ...Liu '535 inherently teaches the limitation of culturing the cells after contacting the cells with the substance, as one of ordinary skill in the art at the time of the invention would have known that time is needed to allow differentiation of the cells and changes in gene expression to take place.

Regarding inherency, MPEP (8th Ed) 2112 provides:

> "To establish inherency, the extrinsic evidence `must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)

The *in vitro* culture limitation of claim 1 is not necessarily present in the method described in Liu. For example, the Liu method could be performed without *in vitro* culture by isolating the stem cells from an animal at the desired stage of differentiation, contacting the isolated cells with the agent, and immediately thereafter assessing modulation of gene expression. Liu admittedly does not make clear what exactly was contemplated in the described method. As cited above, however, "the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference." It does not do so in this case.

The methods of the present specification and Liu are different from one another in several respects in addition to the *in vitro* culturing step discussed above. For example, to analyze gene expression, Liu used the method of differential display involving three different gene profiles. Differential display is a laborious and time-consuming method that analyzes a vast number of genes. This technique is not suited for a high-throughput analysis of a large number of samples. In contrast, the method of the present specification typically involves a PCR-based approach for analyzing cell populations (e.g., two cell populations vs. three expression profiles of Liu) for a finite number of genes and is suitable for high-throughput analyses. The method of the present specification is therefore simpler, quicker, and less expensive to perform than the method of Liu.

Claim 1 is thus believed patentable and in condition for allowance. The dependent claims are believed allowable because of their dependence upon an allowable base claim, and because of the further features recited. Withdrawal of this rejection is therefore respectfully requested.

Rejection Under 35 USC §103

The Office Action rejected claims 2-5 and 10-12 under 35 U.S.C. 103 (a) as being unpatentable over Liu et al. as applied to claim 1, and further in view of U.S. Patent No.

5,874,301 to Keller et al. The Office Action also rejected claim 6 under 35 U.S.C. 103(a) as being unpatentable over Liu as applied to claim 1, and further in view of Thomson et al., Science, 282:1145-1147, 1998 ("Thomson"). Additionally, the Office Action rejected claim 20 under 35 U.S.C. 103(a) as being unpatentable over Liu as applied to claim 1, and further in view of U.S. Patent No. 5,143,854 to Pirrung et al.

The Office Action combined the teachings of Liu with the embryonic stem cells described by Keller to arrive at all the limitations of claims 2-5 and 10-12, the primate embryonic stem cells described by Thomson to arrive at all the limitations of claim 6, and the gene chip technology described by Pirrung et al. to arrive at all the limitations of claim 10. As mentioned above, however, Liu does not teach or suggest any of the steps of independent claim 1. As Keller, Thomson, and Pirrung also do not teach or suggest these limitations, the references, even if properly combinable, do not teach or suggest all the limitations of claim 1. Consequently, all claims depending from claim 1 are necessarily distinguished over those references.

Accordingly, withdrawal of this rejection is respectfully requested.

Conclusion

The claims currently before the examiner are supported throughout the specification and are patentable over the prior art. No new matter has been added. This application is now in full condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any underpayment or credit any overpayment of fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 50-0951.

The examiner is invited to call the undersigned if clarification is needed on any matter within this amendment, or if the examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

AKERMAN SENTERFITT

Dated: February 10, 2009

Stanley A. Kim, Ph.D., Esq.
Registration No. 42,730
Amy A. Ostrom, Ph.D.
Registration No. 52,088
222 Lakeview Avenue, Suite 400
West Palm Beach, FL 33401-6183
Telephone: (561) 653-5000